Expert Opinion

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pH modulation: a mechanism to obtain pH-independent drug release

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Importance of the field: In formulation development, weakly acidic or basic drugs pose a major challenge as the solubility depends significantly on pH of the dissolution media. This gives rise to pH-dependent drug release, as the formulation is exposed to different pH ranges in the gastrointestinal tract. This indicates a need to carry out formulation optimization for such drugs while developing them into a dosage form.

Areas covered in this review: For overcoming pH-dependent behavior of drugs, pH-modifying excipients (which alter the microenvironment pH inside the formulation) are most commonly used. A combination of enteric and sustained release polymers can be used for weakly basic drugs. Other strategies include conversion of crystalline drug to amorphous form, enhancement of partitioning of unionized fraction of drug from the formulation, and using a combination of pH modifier and enteric polymer, micellar solubilization and inclusion complexation.

What the reader will gain: Readers will gain an insight into various formulation techniques for obtaining pH-independent drug release for weakly acidic and basic drugs.

Take home message: Readers will be able to evaluate the different formulation strategies in terms of their applicability and best use of the available strategies when designing their own research work for such drugs.

Keywords: microenvironment pH modulation, organic acids, pH-independent drug release, solubility of weak acids and bases

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1. Introduction

The formulation of a dosage form requires careful manipulation of variables to achieve maximum product efficacy and stability, while minimizing alterations in drug release as a consequence of physiological variables in the gastrointestinal tract (GIT), pH, residence time, intestinal motility or the inherent properties of the drug (solubility, pK_a, pH, molecular size, octanol/water partition coefficient and hygroscopicity) [1].

Drug solubility is one of the critical factors that significantly affect the release profile of a drug from a dosage form. Low drug solubility, in the case of immediate release products, decreases dissolution of drug in the biological fluids and ultimately its bioavailability [2]. Similarly, low solubility, in the case of controlled release formulations, not only affects the dissolution in biological fluids but also decreases the release of drug from dosage form, as the drug has first to be solubilized in the penetrated dissolution media, following which it will diffuse out of the controlled release formulation. This is true for both reservoir and matrix systems, as dissolution of the active compound from the solid dosage form is more rate limiting [3]. Hence,

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Article highlights.

- Strategies using manipulations in external dissolution media are not very useful compared with strategies using formulation optimization.
- Among internal addition strategies the most common strategy is the use of pH-modifying agents that alter the microenvironment pH inside the formulation.
- Alteration in porosity of the formulation, variation in crystallinity of drug and enhancement of partitioning of unionized fraction of drug are also useful strategies for overcoming pH-dependent solubility of drugs.

This box summarizes key points contained in the article.

strategies to improve solubility of such drugs have been devised so as to get the desired therapeutic level. These include salt formation, formulation of inclusion compounds, solid dispersions, prodrugs, and so on [4]. This is true for drugs that have low solubility irrespective of the gastrointestinal pH. However, some drugs show a change in solubility as a function of pH and are said to possess pH-dependent solubility. Examples of such drugs include verapamil hydrochloride, papaverine hydrochloride, dipyridamole, trimethoprim, divalproex sodium, and so on. These drugs when exposed to gastrointestinal pH (pH range 1.2 – 8) show altered drug solubility thus fluctuating drug release throughout the GIT. This indicates that such drugs do not show a pH-independent release profile if formulated as such [5]. Therefore, some formulation optimization techniques have to be adopted for these drugs if a pH-independent release profile is to be obtained.

This review focuses on various strategies that have been used by formulators to obtain pH-independent release from drugs that show pH-dependent solubility. A special emphasis is given to pH modifiers that alter the microenvironment pH (pH_m) of the dosage form and thus help in obtaining pH-independent release. Other strategies that exploit the properties of permeability and erodibility of the formulation have also been discussed.

2. pH-dependent solubility of drugs and their *in vitro* behavior

Most pharmaceutical compounds are weakly ionizable acids or bases or a combinations of these two ionization types. The solubility of non-ionizable compound is a single value that reflects a simple balance between the molar free energy of the solid drug and that of the drug interacting with a polar aqueous solvent. However, for ionizable drug (weak acids [WA] or weak bases [WB]), the ionizability of both the drug and the solvent must be considered [3,6,7]. This implies that the extent of drug ionization would change with extent of solvent ionization (i.e., pH); as a result solid-state to solution-state equilibrium of the drug will also change with pH [7]. The drug solubility is thus a function of pH of the solvent and ionization state of the drug. The solubility, therefore, has to be viewed in the context of pH of the solution at equilibrium and the pK_a values of the compound [6,8]. The pH solubility profile for weakly ionizable compounds can be divided into different regions. **Figure 1** gives the pH solubility profile for WB drugs. It can be described as follows.

1) *The intrinsic solubility region* (~ pH > 7). The compound is completely unionized and has lowest solubility in this pH range.
2) *Ionizing region* (~ pH 4 – 5.5). This region begins around pK_a of the drug. At pK_a the ionized and unionized forms are present in equal concentration in the solution.
3) *pH max region.* This region corresponds to the region of maximum solubility. As the pH is decreased further, the drug is completely ionized and associated with an oppositely charged counter ion.
4) *The salt plateau.* In this pH range the salt solubility prevails and the solubility of compound is almost constant [7].

This solubility profile when interpreted in terms of WB drug incorporated in a dosage form would mean that solubility of basic drug would decrease exponentially with increase in pH as there would be conversion of more ionizable drug to less soluble base [9], leading to precipitation of drug within the matrix and thus a decrease in drug release. This introduces variability associated with gastrointestinal transit or pH-dependent drug release profile [3,10-12]. The opposite would hold true for weak acid drugs, that is, drug solubility would increase as the formulation traveled to the lower part (high pH range) of the GIT [13]. **Table 1** gives a few drugs that demonstrate pH-dependent solubility along with their pK_a values.

These drugs if formulated as such will give pH-dependent drug release rather than the much more desirable pH-independent release profile. Tablets containing verapamil hydrochloride (WB) in ethyl cellulose (EC) matrix have been shown to release 83% of drug after 8 h in 0.1 N HCl (pH 1.2), whereas only 34% was released in phosphate buffer (pH 6.8) [14]. The solubility of verapamil is high in 0.1 N HCl owing to its conversion to the ionized state at this pH. However, its solubility in phosphate buffer (pH 6.8) decreases as it is converted to the unionized state. Thus, a 2.5-fold difference in drug release was observed at pH 1.2 as compared with that at pH 6.8 [14,15]. This study indicated the need to develop strategies that would overcome the effect of inherent solubility and help in obtaining a pH-independent drug release profile for such drugs.

3. Strategies to overcome pH-dependent solubility of drugs

Strategies to overcome pH-dependent solubility can be broadly classified as follows.

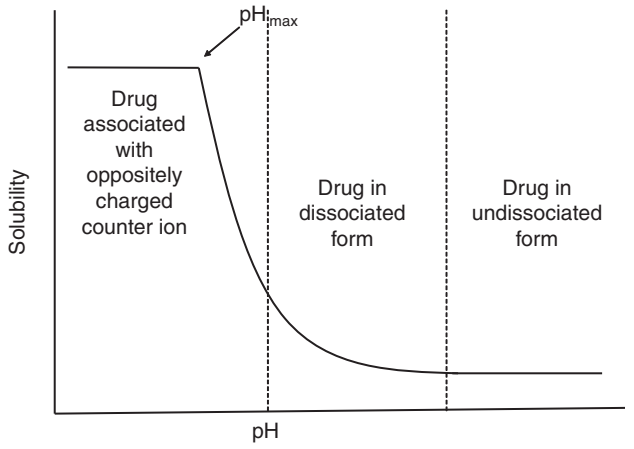

Figure 1. pH solubility profile for a compound with basic pK_a.

3.1 External addition

The term external addition refers to inclusion of certain substances (surfactants and complexing agents) in the external dissolution media in order to improve the solubility of drugs. Sheng *et al.* studied the effect of incorporation of sodium lauryl sulfate (SLS) into dissolution media on the solubility of WA drug ketoprofen. SLS at its critical micelle concentration forms micelles, which solubilizes the drug. Micellar solubilization can occur in the ionized as well as the unionized state of the drug, leading to an increase in solubility irrespective of the dissolution pH. An increase in SLS concentration (0.5 – 2% w/v) led to an increase in solubility and intrinsic dissolution rate of the drug. At the highest SLS concentration (2% w/v), the equilibrium solubility ranged from 13.04 ± 0.04 to 58.80 ± 0.01 mg/ml, and the intrinsic dissolution rate varied from 9.20 ± 0.16 to 84.9 ± 2.89 mg/(cm^2 s^{½} rad^{½}) in the pH range 4.0 – 6.8. This indicated that both the parameters were dependent on pH [16].

In another study, the relative effectiveness of different surfactants as solubility enhancers was studied on poorly water-soluble acidic drug (mefanamic acid). The surfactants used were cetyltrimethylammonium bromide (CTAB) (cationic surfactant), SLS (anionic surfactant) and polysorbate 80 (non-ionic surfactant). An increase in dissolution of drugs was observed with all the surfactants in acidic as well as in alkaline media, the maximum being with CTAB. The absorption spectrum of mefanamic acid shifted from 285 to 294.5 nm in the presence of CTAB, thus indicating a change in microenvironment polarity of drug resulting from penetration of drug into CTAB micelle [17]. In this study, although the dissolution of mefanamic acid increased, drug release was still pH-dependent [18].

Another technique used for increasing solubility by manipulation of the external environment is by the formation of inclusion compounds. Cyclodextrins are commonly used for this purpose. Riis *et al.* studied the dissolution of 8-Prenylnaringenin (a WA drug) in the presence of hydroxypropyl-β-cyclodextrin (HP-β-CD). It was hypothesized that HP-β-CD would form an inclusion compound with the drug and thus enhance its solubility. However, this strategy did not work out well and pH-independent drug release was not obtained. It was observed that only a small amount of HP-β-CD could penetrate the formulation matrix and solubilize the drug, and thus could increase the drug release only to a limited extent. Furthermore, the slight increase in solubility of the drug by HP-β-CD was not a function of pH of the dissolution media and thus again led to pH-dependent solubility [19]. Similar studies carried out by Kranz *et al.* have also shown that the inclusion of HP-β-CD could increase the solubility of the drug, but to a limited extent (1.83 times increase) [20]. From the above discussion it is clear that solubility within the matrix is the critical parameter that determines the drug release behavior. Thus, external addition is not a very useful approach to overcome the pH-dependent solubility behavior of the drugs. Therefore, a better approach to increase the solubility would be adjustment of the microenvironment pH within the formulation [19].

3.2 Internal addition

Internal addition refers to incorporation of certain excipients within the formulation so as to improve the solubility of the WA or WB drug. The main strategies that have been used to obtain pH-independent release by internal addition of excipients are depicted in **Figure 2**.

3.2.1 Strategy I: adjustment of pH$_m$ by incorporation of pH modifiers

Microenvironment pH can be described as the pH of saturated solution in the immediate vicinity surrounding drug particles [21,22]. pH modifiers alter the pH in the microenvironment and thus bring the pH inside the formulation to a value where drug solubility is higher. This increases the drug dissolution and release irrespective of the pH of the external dissolution media.

The solubility of completely 'unionized' drug (S_o intrinsic solubility) can be related to the solubility measured at a given pH (S) and pK_a of the compound by the Henderson-Hasselbach equation. The expression for this equation for monobasic compounds is

$$S = S_o\left[1+10^{(pk_a - pH)}\right]$$

and for monoacidic compounds is

$$S = S_o\left[1+10^{(pH - pk_a)}\right]$$

Thus, it can be seen that solubility of an acid increases at pH values greater than pK_a. For bases, solubility increases with decreasing pH at values less than pK_a [7,23-25]. Therefore, solubility of WB can be increased by decreasing pH of the microenvironment by the use of organic acids such as adipic,

Table 1. Solubility data and pK_a values of a few drugs that demonstrate pH-dependent solubility.

Drug name	pK_a	Solubility profile	Ref.
Verapamil hydrochloride	8.6	> 100 mg/ml at pH < 6.35 50 mg/ml at pH 6.45 2.71 mg/ml at pH 6.8	[14,56]
Dipyridamole	6.1	29.9 mg/ml at pH 2.5 18.2 mg/ml at pH 2.9 0.54 mg/ml at pH 4 0.013 mg/ml at pH 6 0.005 mg/ml at pH 7	[57-59]
Oxybutanin hydrochloride	8.04	754 mg/ml at pH 1.2 1.24 mg/ml at pH 6.8 0.0241 mg/ml at pH 10.2	[30,60]
4-Amino pyridine	9.4	95 mg/ml in 0.1 N HCl 78 mg/ml in phosphate buffer	[45,61]
Felbinac	4.3	10 mg/ml at pH 1.2 5000 mg/ml at pH 7.5	[62]
Vinpotecine	7.1	11.93 μg/ml at pH 6.2 3938.67 μg/ml in 0.1N HCl	[35]
Divalproex	4.6	1 mg/ml at pH 1.0 200 mg/ml at pH 6.8	[38]
Indomethacin	4.5	2 μg/ml at pH 1.2 25 μg/ml at pH 5.1 190 μg/ml at pH 6.0 1600 μg/ml at pH 7.2	[39,63,64]
Telmisatran	4.45	520.55 μg/ml at pH 1.2 0.28 μg/ml at pH 6.8 0.09 μg/ml in d. water 491.56 μg/ml at pH 10	[21,65]
Propranolol	9.5	225 mg/ml at pH 1.2 130 mg/ml at pH 6.8 36 mg/ml in d. water	[66,67]
Glipizide	5.9	1.1 μg/ml at pH 2 1.3 μg/ml at pH 4.4 4.9 μg/ml at pH 5.8 26.6 μg/ml at pH 6.8 280.7 μg/ml at pH 8 898.9 μg/ml at pH 10	[68]
Ketoprofen	4.76	0.28 mg/ml at pH 4 0.49 mg/ml at pH 4.6 3.08 mg/ml at pH 6 40.76 mg/ml at pH 6.8	[16]

d.: Distilled.

fumaric, tartaric and succinic acid [9,26], and that of WA can be increased by increasing pH of the microenvironment by the use of basic excipients such as dicalcium phosphate (DCP), magnesium oxide (MgO) and magnesium hydroxide ($Mg(OH)_2$) [27].

3.2.1.1 Organic acids as pH modifiers

Organic acids have been widely used to modulate the release of WB drugs. These organic acid-containing formulations absorb water when they come in contact with dissolution media. In acidic media, the organic acid serves as inert filler and drug diffuses out owing to its inherent high solubility. However, in alkaline pH, organic acids dissolve to decrease the pH of the microenvironment and create an acidic drift in the direct vicinity of the drug [26,28,29]. This increases the solubility of the drug, thus leading to a higher concentration gradient and a higher driving force for diffusion [14]. The net result is that the drug releases independently of the pH and the desired pH-independent release effect is obtained. However, the duration and extent of pH modulation by organic acid depend on its physicochemical properties, which include acid strength and aqueous solubility [28]. Ideally, organic acids should have increased acid strength (low pK_a) and relatively low solubility in the lower pH range so that they can provide low pH in the matrix for longer periods even when added in low proportions in a formulation, that is, have greater residence time in the matrix [30]. Varma *et al.* demonstrated pH-independent release from oxybutynin hydrochloride tablets containing fumaric acid (FA) as pH modifier. It was observed that at a concentration of 10% w/w FA a pH-independent release was obtained [30]. The physicochemical properties of different pH modifiers are summarized in **Table 2**.

The relative effectiveness of pH modifiers can be evaluated by three different parameters: i) measurement of residence time of organic acid in the formulation; ii) measurement of pH_m; and iii) measurement of percentage release of organic acid from the formulation.

1) *Measurement of residence time.* Siepe *et al.* compared the relative efficacy of FA and succinic acid (SA) on the release of dipyridamole from press-coated tablets by measuring the residence time of the acid in the formulation. SA has a higher solubility than FA in both pH 1.2 and pH 6.8 (**Table 2**). As a result SA leached out of the formulation after 4 h whereas FA, because of its low solubility, remained in the formulation and could effectively control the pH for 6 h, thereby indicating FA to be a better organic acid than SA for improving drug release [22]. Similarly, in another study the residence time of FA was found to be 2 h as compared with that of SA, which leached out after 1 h, when dipyridamole was formulated into hydroxypropyl methylcellulose (HPMC)-based matrix minitablets with FA or SA as pH modifiers [26]. These studies indicated that the greater the residence time of the organic acid in the formulation, the better the efficacy of that acid.
2) *Measurement of pH_m.* pH in the microenvironment can be measured by various methods. Indicator dyes that change color with a change in pH play a special role in pH_m measurement. These dyes can be incorporated into the formulation. For example, thymol blue, which is red at pH < 2.8 and yellow at pH > 2.8, was used by Varma *et al.* for measuring the acidity of oxybutynin matrix tablets containing FA. It was observed that the tablets' core remained red for 8 h, demonstrating pH < 2.8 when FA (10% w/v) was used [30]. Other indicator dyes that have been used include methyl red [14] and bromophenol blue [26]. In addition to

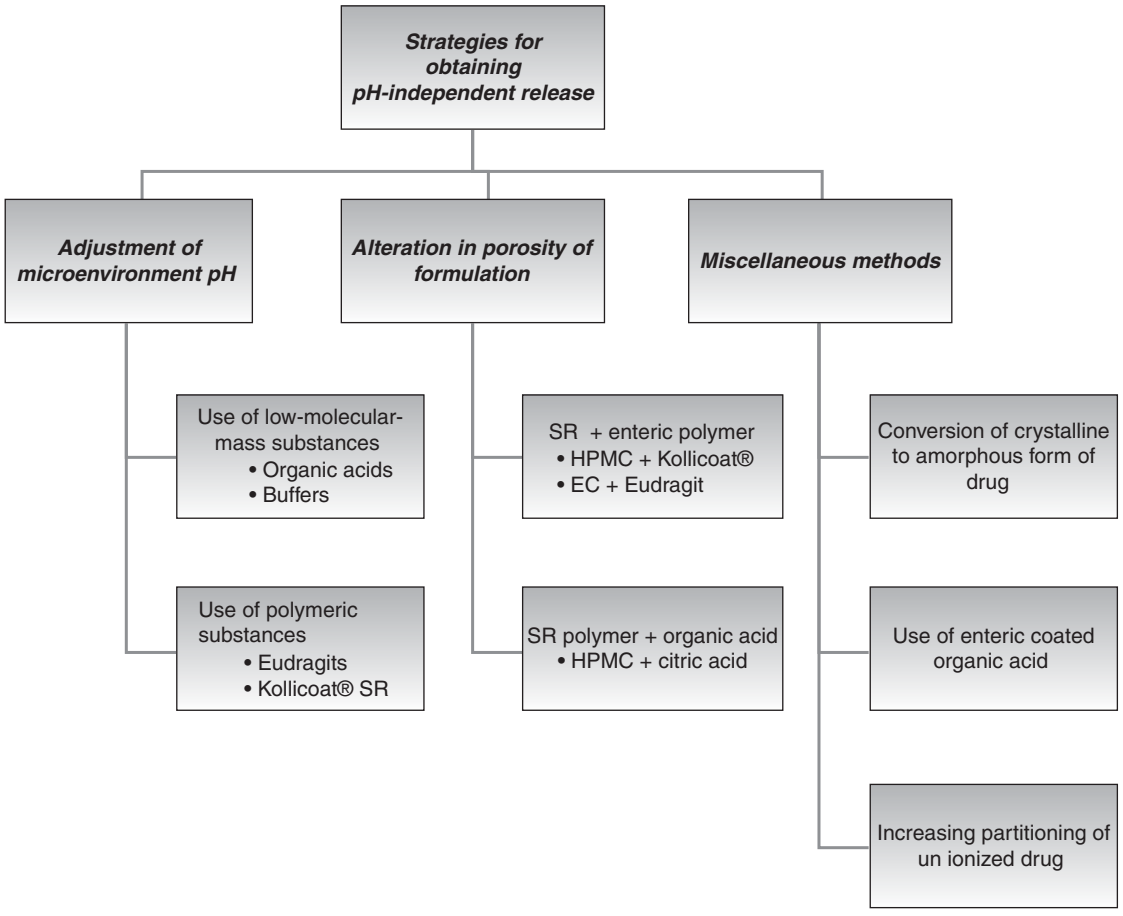

Figure 2. Strategies for the development of pH-independent release from drugs with pH-dependent solubility: internal addition.
SR: Sustained release.

indicator dyes, instrumental methods have also been used for the measurement of pH_m. These include use of surface pH electrode [21,26], confocal laser scanning microscopy [31], nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) [32-34] and EPR imaging (EPRI) [28].

3) *Measuring percentage release of organic acid.* The amount of organic acid released in the dissolution media can be correlated to the relative efficacy of organic acid. The greater the amount of organic acid released the lesser would be the amount of acid that would be available within the matrix to control pH and the lower would be the efficacy of the pH modifier. Also, the release of organic acid is directly proportional to its solubility. For example, Siepe *et al.* studied the release of dipyridamole from matrices containing organic acids (FA, citric acid [CA], SA and adipic acid [AA]) (20% w/w). After 4 h of dissolution CA and SA were almost completely released (CA – 95.6%, SA – 93.9%), whereas a significant amount of the initial amount of FA (28.4%) was still present. The drug release values correlated with the order of organic acid released. It was highest with FA (86.6%), followed by CA (65.6%), SA (51.7%) and AA (41.8%) after 6 h of dissolution. The presence of either CA or FA in the formulation created an acidic and favorable environment, thus resulting in a rapid drug release profile [28].

All the above studies demonstrated that FA is most effective in modulating the pH_m as it has higher acid strength (low pK_a) and lower solubility, as a result of which it remains in the matrix for a longer period of time and is able to replenish the lost acid from the matrix and decrease pH_m over a longer period of time. The rank order of efficacy of other organic acids in terms of maintaining pH_m was found to be FA > CA > SA > AA [14,22,26,28]. Different studies have also elucidated the concentration of FA that must be used in order to obtain pH-independent drug release. Varma *et al.* demonstrated that incorporation of 10% w/w FA was sufficient to overcome pH-dependent solubility. However, when a lower

Table 2. Physicochemical properties of different pH modifiers.

Organic acid	pK_{a1}	pK_{a2}	Solubility in pH 6.8 (mg/ml)	Solubility in 0.1 N HCl (mg/ml)	Ref.
Fumaric acid	3.03	4.54	10	4.5	[28,56,59]
Citric acid	3.1	–	651.9	608.8	[28]
Succinic acid	4.2	5.6	72.5	66.6	[28,59]
Ascorbic acid	4.2	–	301.5	296.1	[59,69]
Sorbic acid	4.76	–	> 100	2.32	[56]
Adipic acid	4.41	5.28	> 100	< 30	[56]

concentration (5% w/w) was investigated, it did not lead to pH-independent release, though it did increase the release in phosphate buffer. The reason for this was probably that the amount of FA available as buffer ingress into the formulation was not sufficient to maintain pH_m at the desired level [30]. Shufang *et al.* demonstrated that pH-independent release of vinpocetine from HPMC matrix tablets could be attained at 22.5% w/w FA concentration [35], whereas in another study 20% w/w FA concentration was found to provide the desired result. Further, the drug release increased as the amount of FA added increased, but to a limiting value of 40% w/w, after which any further increase of FA concentration had no effect [36,37]. However, Streubel *et al.* reported that an increase in release of verapamil hydrochloride by FA is independent of concentration of FA used, but it is to be noted that concentrations used in their study were much higher than those used by other researchers [14].

Studies carried out by Siepe *et al.* showed that a high concentration of organic acid (> 40% w/w), besides causing a reduction in microenvironment pH, can also influence osmotic pressure, and alter swelling dynamics, gel properties or hydration behavior [22]. Thus, it can be concluded that, while formulating a dosage form for WA and WB, several factors have to be considered. **Figure 3** represents some of the factors that influence formulation design for such drugs.

3.2.1.2 *Basic excipients as pH modifiers for weakly acidic drugs*

Basic excipients can be used for improving the solubility of WA drugs. These dissolve in acidic media, where the drug solubility is less, thereby raising the pH and converting the unionized less soluble form of drug to the ionized form and increasing the drug solubility and thus the release. Rao *et al.* compared the relative efficacy of two pH modifiers, namely DCP and Eudragit E-100, on the release of WA drug divalproex sodium. The drug was incorporated into extended release (ER) matrix of methocel K4 M. The concentration of both the pH modifiers taken was 35% w/w. Incorporation of these two excipients led to an increase in drug release but the release profile in pH 1.2 was still slower as compared with that in pH 6.8 when DCP was used as the pH modifier. However, a pH-independent release was observed with Eudragit E-100. To investigate the reason for this differential behavior, equal quantities of both the modifiers were dissolved separately in 0.1 N HCl and pH of the solution was measured. The pH of the solution of Eudragit (140 mg/ml) was 6.7 as compared with pH 3.8 of DCP (140 mg/ml). Thus, it was concluded that DCP was less useful because of its inability to alter the pH, limited buffering capacity, small molecular mass and high solubility in acidic media [38]. Riis *et al.* obtained pH-independent release of WA drug 8-Prenylnaringenin using MgO as the alkalizer. They also established that water-insoluble alkalizers (MgO, $Mg(OH)_2$ and magnesium trisilicate) were better than water-soluble (sodium carbonate and sodium citrate) alkalizers in obtaining pH-independent release [19].

Similarly, Tirkkonen *et al.* formulated microcapsules of indomethacin to obtain pH-independent release. The dissolution of indomethacin decreases the microenvironment pH inside the microcapsules and thus decreases its own solubility. This self-buffering action influences the dissolution of drug. To overcome this self-buffering action and to obtain pH-independent release, buffering agent disodium phosphate (DSP) was added into the microcapsules. DSP dissolved to elevate the pH inside the microcapsules, which prompted the drug to dissociate and thus increase its water solubility. Increasing DSP content increased the release and the self-buffering effect was overcome when DSP concentration was found to lie between 37.5 and 50% w/w. However, the study concluded that in addition to modulation in microenvironment pH, change in porosity of the matrix was also a controlling factor. The scanning electron microscopy study on the microcapsules showed that the capsule membrane remained intact when the microspheres contained no or an insignificant amount of DSP. By contrast, numerous holes and ruptures were formed in the coating with moderate (10 – 25% w/w) and large (37.5 – 50% w/w) amounts of DSP owing to osmotic imbibation of water leading to enhanced release [39].

Espinoza *et al.* reported that the mechanism by which acidic excipients modulate drug release is not by microenvironment pH modulation but solely by enhancement of porosity of the formulation. An improved dissolution rate of pelanserin hydrochloride was observed when CA was incorporated into drug HPMC matrix. It was found that

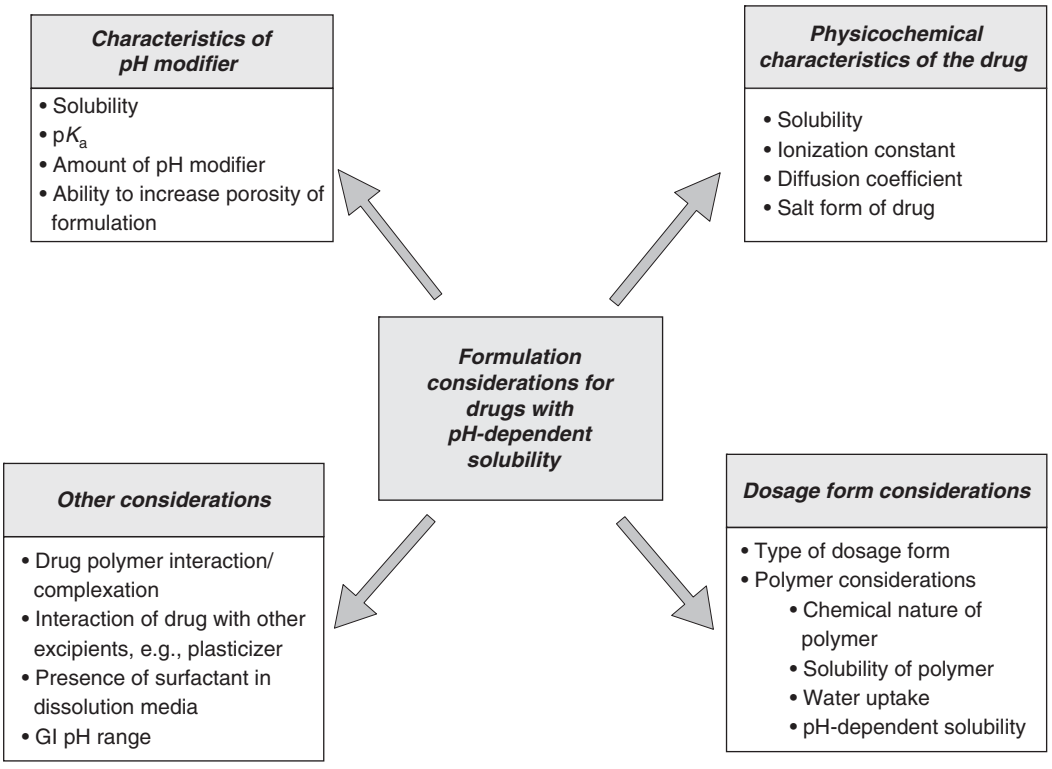

Figure 3. Factors to be considered while formulating weak acid and weak base drugs into dosage form along with a pH modifier.
GI: Gastrointestinal.

CA behaved simply as a hydrosoluble excipient and leached out of the matrix in a short duration of time to increase the porosity and decrease the tortuosity, thus allowing faster release. In this case no effect on pH_m was observed when CA was incorporated into the matrix [36]. However, many other authors have contradicted these findings and stated that pH_m modulation is the basic mechanism when using organic acid or basic excipients in altering release of drugs with pH-dependent solubility [30,26,28].

3.2.2 *Strategy II: using enteric polymer along with water-soluble/insoluble polymer*

This strategy works on the principle of enhancement of permeability of the dosage form to counteract decreasing solubility [13]. This approach has been used for WB drugs. In acidic media, enteric polymer is insoluble and acts as part of the formulation and thus contributes to retardation of drug release. In intestinal fluids, it dissolves and leaches out, thus making the dosage form more permeable, thereby increasing drug release and giving rise to pH-independent release [13,40].

Dashevsky *et al.* investigated coating of verapamil layered pellets with enteric polymer and insoluble sustained release (SR) polymer. The SR polymer used was Kollicoat® SR 30D (BASF, Germany) (an aqueous dispersion of polyvinyl acetate) and the enteric polymer used was Kollicoat® MAE 30DP (an aqueous dispersion of methacrylic acid and ethyl acrylate copolymer; methacrylic acid copolymer type C). Coating of pellets was done in three different ways (**Figure 4**): sequential coating: ER polymer (Kollicoat SR 30D) coating followed by top coating of enteric polymer (Kollicoat MAE 30DP); sequential coating: enteric polymer followed by top coating of ER polymer; and coating with a blend of ER and enteric polymer.

When the pellets were coated with the first approach the drug release in 0.1 N HCl decreased owing to an increase in diffusional resistance as both the polymers were insoluble in this medium, whereas in phosphate buffer pH 6.8 the release increased as the enteric top coating dissolved, allowing the drug to release out through a single layer of ER polymer. pH-independent release was obtained with a pellet coating of 10% Kollicoat SR 30D and a top coating of 5% Kollicoat MAE 30DP, and also at 15 and 4% of the respective polymer concentration. pH-independent release was also obtained with the second approach at 5% coating level of Kollicoat MAE 30DP and a second coating of 5 or 10% Kollicoat SR 30D. In this case at pH 6.8, the drug diffusion was through two layers, in comparison with the first approach, where diffusion occurred through a single layer. This was because dissolution of enteric polymer occurred to increase the overall permeability, but it could not diffuse out through the outer

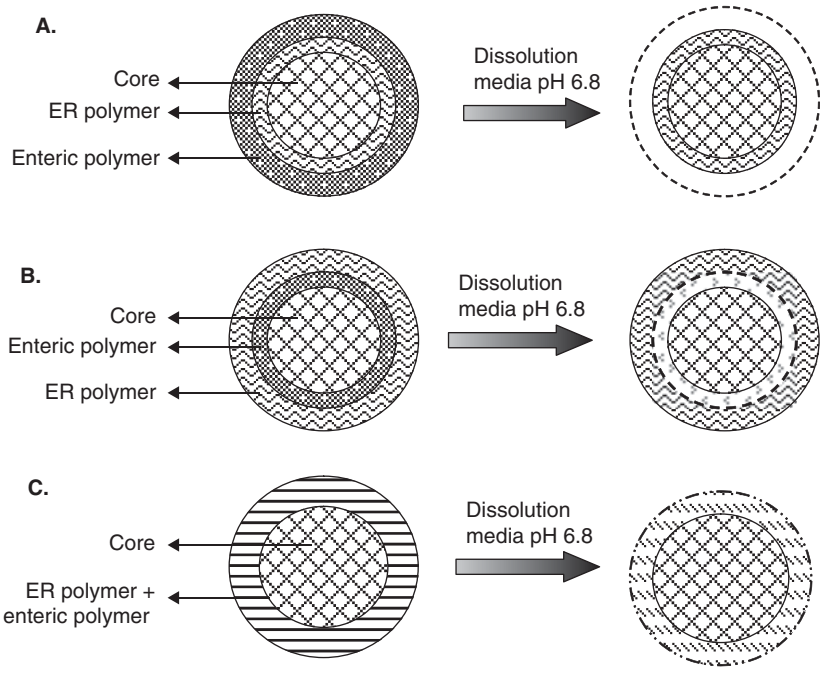

Figure 4. Schematic representation of different coating layers and their behavior in dissolution media. A. ER polymer (Kollicoat® SR 30D) coating followed by top coating of enteric polymer (Kollicoat® MAE). **B.** Enteric polymer followed by top coating of ER polymer. **C.** Coating with a blend of ER and enteric polymer.
ER: Extended release.

coating of SR polymer (**Figure 4**). In addition, the dissolved entrapped enteric polymer also created an acidic microenvironment pH, keeping the solubility and concentration gradient high. The third approach, which involved simultaneous coating of the two polymers, was found to be least suitable as the two polymers were incompatible with each other. They coagulated and flocculated in contact with each other. Thus, pH-independent release of verapamil hydrochloride was obtained using a sustained release and an enteric polymer using the first two approaches, at a particular coating level [13].

Similarly, Amighi *et al.* obtained pH-independent release from pellets containing WB drug UCB 11056 by using blends of insoluble neutral Eudragit NE 30D and enteric Eudragit L 30 D55 in a ratio of 7:3 [41]. In another study, Lecomte *et al.* achieved pH-independent release of propranolol hydrochloride from pellets coated with blends of ethyl cellulose and Eudragit L (75:25) [40].

Streubel *et al.* formulated matrix tablets of verapamil using a combination of enteric polymer, hydroxypropyl methylcellulose acetate succinate (HPMCAS), with either water-insoluble ethyl cellulose or water-soluble HPMC as SR polymer [14]. It was postulated that HPMCAS, being insoluble in 0.1 N HCl, would act as a diffusion barrier in this medium and control drug release, whereas it would dissolve and act as a pore former and accelerate drug release in alkaline medium and thus compensate the effect of reduced solubility. When EC was used in concentrations as high as 80:20 (EC: HPMCAS), tablets did not show pH-independent release. This was attributed to the fact that addition of HPMCAS to EC matrix caused a reduction in pore size of the matrix as compared with plain EC matrix, which prohibited the drug from leaching out. Further, the presence of poorly water-soluble drug on the matrix surface prevented HPMCAS from leaching out of the matrix (only 28% leached out after 8 h at pH 7.4 and no HPMCAS was released in 0.1 N HCl), leading to pH-dependent behavior. In matrices containing water-soluble HPMC along with HPMCAS, the release decreased because the dissolution of high-molecular-mass HPMCAS was hindered at pH 6.8 in the presence of a HPMC gel network. The pores in the dosage form were unable to accommodate diffusing HPMCAS macromolecules. Also, according to free volume theory of diffusing macromolecules [42], if HPMCAS and drug have to diffuse out of the formulation, then porosity of the matrix has to be increased, which in this case would occur by rearrangement of a large number of HPMC monomer segments. However, in this study rearrangement of HPMC monomers could not occur to the desired level owing to gel formation by HPMC. Therefore, with both HPMC and EC the drug profiles in both the media did not match and pH-independent release could not be achieved [14]. The above studies indicate that the use of polymer blends for augmentation of drug release by enhancement of porosity depends on both the physiochemical properties, such as water uptake and erodibility (which in turn depends on 'reptation' of polymers [37,43]), and gel formation [40] by SR polymer.

3.2.3 Strategy III: miscellaneous methods

The other methods that have been used to overcome pH-dependent solubility of WA and WB drugs are listed below.

3.2.3.1 Formulation of drug into solid dispersion along with alkalizer

The dissolution of model drug telmisartan was improved by incorporating it into a solid dispersion of PEG 6000 along with an alkalizer [21]. Telmisartan is an antihypertensive and is readily ionisable, and subsequently the solubility is pH-dependent. The solubility is high in strongly acidic (521.55 µg/ml at pH 1.2) and basic (491.56 µg/ml at pH 10) conditions but very low (0.09 µg/ml in water) under neutral conditions. Tran *et al.* used sodium bicarbonate ($NaHCO_3$), bentonite, disodium hydrogen phosphate (Na_2HPO_4), arginine, MgO and sodium carbonate (Na_2CO_3) as alkalizers. The drug release in 0.1 N HCl was found to be 100% irrespective of the alkalizer used as the solubility of the drug in this medium was high; but the differentiation between alkalizers became apparent in intestinal media pH 6.8 and water. $NaHCO_3$ caused a moderate increase in release whereas bentonite, Na_2HPO_4 and arginine did not have any significant effect. The use of MgO and Na_2CO_3 caused the greatest enhancement of drug release (as shown in **Figure 5**). To understand the mechanism by which dissolution was improved, pH_m was measured in various tablets. The pH_m values (**Figure 5**) of tablets containing bentonite, Na_2HPO_4 and arginine were not high enough to reach the basic environment in the tablet, thus accounting for lower release. Basic pH was reached in MgO, Na_2CO_3 and $NaHCO_3$ in decreasing order. The release increased as the amount of modifier was increased. However, it was observed that the increase in dissolution rate did not correlate proportionally with increasing microenvironment pH, thus suggesting involvement of some other mechanism. It was found using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FTIR) that there were changes in drug crystallinity. The DSC studies revealed that in the presence of PEG 6000 the drug was converted to a partially crystalline state. The PXRD and FTIR results proved this further, and showed that incorporation of alkalizer converted the partially crystalline form to a completely amorphous form, leading to further enhancement of dissolution. The differential behavior of different alkalizers was also correlated to altered crystallinity. The formulations in which the drug was in a partially crystalline form showed less dissolution, whereas the dissolution increased as the drug changed to a completely amorphous form [44]. The FTIR studies established the performance of MgO to be the best [21].

3.2.3.2 Use of enteric citric acid

A WB experimental drug, 4-aminopyridine was taken as a model to obtain zero-order release using enteric citric acid (ECA) from HPMC matrices. ECA was incorporated into the matrix in increasing proportions (2 – 9%) to elucidate the concentration at which zero-order release was obtained. In acidic media ECA is insoluble and therefore acted as a physical barrier and decreased the surface available for drug diffusion and water transport and also increased tortuosity of the diffusional path, leading to a decrease in drug release in acidic media. In alkaline pH, enteric coating of ECA dissolved creating voids in the matrix, thereby increasing the porosity and decreasing the tortuosity of the matrix. This allowed faster water penetration and thus greater drug release. At 10% w/w ECA concentration the drug release curve flattened, indicating an apparent zero-order release rate as compared with the parabolic curve for formulations without ECA. The reduction in degree of curvature of the release profile occurred as a result of two factors: reduction in release rate in the first hour (dissolution in acidic media); and increase in release rate in the second part of the process (dissolution in alkaline media) [45].

3.2.3.3 Increasing partitioning of drug

Sutinen *et al.* obtained pH-independent release of timolol maleate incorporated into silicone microspheres by increasing the partitioning of unionized fraction of drug from the microspheres. The release was found to be only 20% when the drug was incorporated into pla*in silico*ne microspheres. To enhance the drug release, pH-adjusting agents (monosodium phosphate, disodium phosphate and trisodium phosphate) were incorporated into the microspheres and it was observed that the rate of drug release from these microspheres was 3.3 – 8.2 times higher as compared with plain microspheres. In this study, the drug release was controlled by partitioning of unionized drug from the matrix. The incorporation of pH-adjusting agents raised the pH inside the microspheres and as a result most of the drug fraction remained unionized (timolol $pK_a \sim 9.3$ [46]) and hence could partition out of the formulation, leading to greater release. The extent of unionized fraction maintained in the formulation by pH modifiers (buffers) depends on its basic nature. Therefore, trisodium phosphate, which had the highest basic strength, accelerated the rate of release to maximum because a greater fraction of drug remained in the unionized state and hence could partition out easily. The rank order of effectiveness of pH modifier was monosodium phosphate < disodium phosphate < trisodium phosphate. The drug release was thus independent of pH [47].

4. Conclusion

The above studies have demonstrated that for improving the dissolution of WA and WB drugs and obtaining pH-independent release, adjustment of the microenvironment pH of the formulation using acidic or basic excipients is the best approach and has been widely used by formulators. Although strategies exploiting the

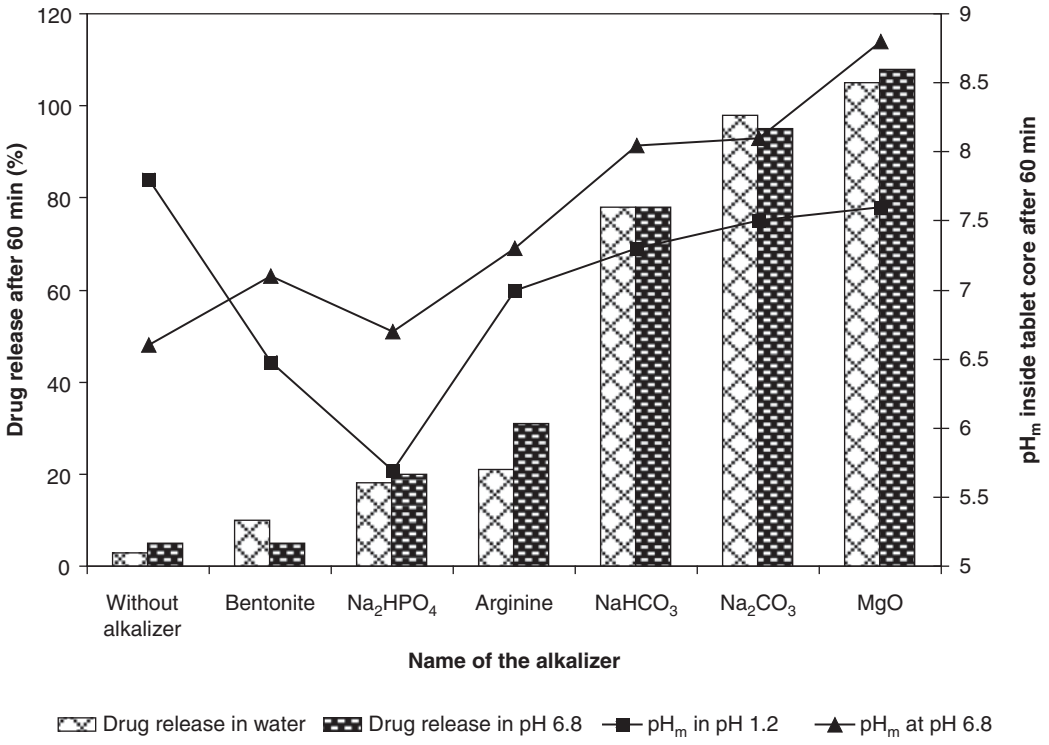

Figure 5. A comparison of the percentage drug release values of telmisartan and the corresponding pH_m obtained when using different alkalizers.

MgO: Magnesium oxide; Na_2HPO_4: Disodium hydrogen phosphate; $NaHCO_3$: Sodium bicarbonate; Na_2CO_3: Sodium carbonate; pH_m: Microenvironment pH.

permeability of the dosage form have also been used, they involve a lot of formulation optimization in terms of concentration of permeability-enhancing polymer or low-molecular-mass excipient and other formulation considerations, therefore they have not been preferred. However, formulation approaches that use both the mechanisms, that is, microenvironment pH modulation and porosity enhancement, could be useful.

5. Expert opinion

In formulation development, WA or WB pose a major challenge as the solubility depends significantly on pH of the dissolution media. This article has focused on overcoming the above-mentioned challenge, thereby leading to the development of formulations giving pH-independent release.

pH-independent release can be obtained by modulating the porosity and erodibility of the formulation by using polymer coating, or by changing drug characteristics. Polymer coatings suffer from the drawbacks of requiring careful alteration of the amount of coating level and the percentages of enteric and SR polymer that have to be used. Approaches using manipulation of drug crystallinity and partitioning behavior are drug- and formulation-specific, and cannot be used for all kinds of WA and WB drug. Therefore, use of pH modifiers (acidic or basic excipients) was found to be the most effective and commonly used approach.

The wide applicability of pH modifiers makes this research area potentially important. This is because these strategies are applicable to most of the pharmaceutical compounds. These strategies are also applied to conventional tablet and capsule dosage forms, which are commercially still the most widely used dosage form in comparison with new drug delivery systems, whose commercial viability and profitability are yet to be fully established although they have immense potential. Therefore, this research can be used on a commercial scale as well. Further, this research has also been extended to include areas of new drug delivery systems such as microspheres [39,47], transdermal patches [48], and so on.

This area, however, lacks extensive research in terms of factors that influence the strategies used that ultimately affect the design of dosage form and release characteristics of the drug. For example, before an organic acids is used a knowledge of solubility and pK_a of organic acid, threshold level at which the organic acid will start showing its buffering action, compatibility of organic acid with other ingredients, influence of organic acid on viscosity of SR polymer, effect on overall osmotic pressure of the formulation, and so, is required.

The scope of using pH-modifying excipients is not limited to obtaining pH-independent release, but is expanding into

other areas of pharmaceutical development. The following examples illustrate the applications of pH modifiers.

1) pH modifiers are being used for sustaining the drug release. These agents alter the microenvironment pH and bring the pH to a value where polymer ionization is suppressed, leading to a decrease in the solubility of the polymer, which in turn leads to a decrease in polymer erosion and sustained release [49].
2) Citric acid is used as a plasticizer in extrusion spheronization methods for developing colon-targeted drug delivery systems [50-53].
3) pH modifiers can be used to improve stability of the formulation [54,55].

Therefore, considering the present discussion, the area of pH modifiers dealing with microenvironment pH modulation is very interesting. This is because the actual physical laws (solubility) are being applied to the development of the formulation. Thus we see the art of formulation merging into the science of physical laws to give a result that is useful, cost-effective, does not require complex processing steps and, overall, aims to provide therapeutic benefit in the form of pH-independent release.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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